The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986). Thus, according to applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 227 U.S.P.Q. 293 (C.A.F.C. 1985).

First, with respect to the rejection on page 2, paragraph 5 of the Office Action, claims 31 and 71 were rejected for indefiniteness of the terms "modulating" and "modulates," because, according to the Examiner, it is unclear what type of modulation is intended, *i.e.*, increasing or decreasing the amount of an immune response.

With respect to claims 31 and 71, Applicants respectfully disagree with the Examiner and assert that the term "modulate", as used in the specification as filed, encompasses both increasing and decreasing activity. Applicants respectfully point out that page 17, lines 25 to 30, provides a general disclosure of modulating an immune response, and page 9, line 2 of the specification as filed provides literal support for the terms "increase" and "decrease" in relation to T cell activation assays. In particular the Examiner's attention is drawn to page 30, lines 24 and 25, of section 5.2, "modulate" is generally defined as "interfere or enhance," which one of skill in the art would clearly understand to mean increase or decrease, respectively. (Although section 5.2 relates to screening methods, one of skill in the art would clearly recognize the general meaning of this term is applicable to instances of modulation disclosed in other sections of the application, including those which teach modulation of an immune response.) Additionally, the concept of a compound that interferes with, *i.e.* decreases, the destructive immune response responsible for the autoimmune disorder is taught at page 26, lines 19 to 36, in connection with screening for anti-autoimmune compounds. The concept of increasing or eliciting an immune response against an infectious disease antigen, for example, is found throughout the specification (see for example, page 17, line 24, wherein stimulation, *i.e.*, increase, of an immune response, is taught). Thus, the specification defines the term "modulate", as meaning either increasing or decreasing, in this case, immune response activity.

However, despite Applicants' traversal of the rejection of claim 31, claim 31 has been amended to recite "decreases" instead of "modulates." Thus, Applicants submit that the

rejection is overcome with respect to claim 31 and the rejection should be withdrawn with respect to claim 71 for the reasons discussed above.

Second, on page 3, paragraph 6, of the Office Action, claims 75 and 76 were rejected for indefiniteness of the term "activity," because, according to the Examiner, it is unclear what type of activity is to be either increased (claims 75) or decreased (claim 76).

Applicants assert that claims 75 and 76 have a clear and definite meaning with regard to the term "receptor activity" when construed in the light of the specification. Given the numerous examples of "receptor activity" disclosed in the text, one of skill in the art would be able to comprehend with clarity the meaning and scope of the term "receptor activity" of claims 75 and 76. Examples of alpha (2) macroglobulin receptor activities include binding activity, antigen presentation, endocytosis, activation of cytotoxic T cell activity, cell signaling activities, and chemotactic activities (see page 30, line 35 through page 31, line 3; page 36, lines 9-13; page 28, lines 25-32; page 30, lines 7-12; and page 35, lines 7-26). Thus, the specification as filed provides a clear definition of alpha (2) macroglobulin "receptor activity."

Third, on page 3, paragraph 7 of the Office Action, claim 83 was rejected for indefiniteness of the term "small molecule," because according to the Examiner, the metes and bounds of the claim are unclear.

Applicants respectfully disagree. At page 39, lines 6-22, Applicants cite references, for numerous organic and inorganic, synthetic and natural small molecules that can be purchased as libraries. Thus, one of skill in the art would be able to determine the meaning of the term "small molecule." Therefore, the metes and bounds of the claim are clear.

In view of the forgoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

2. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 31, 32, 71, 75, and 77-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with theses claims. The Examiner contends that the specification, while being enabling for modulation in terms of decreasing the binding of a ligand to the alpha 2M receptor and hence affecting receptor activity, does not reasonably provide

enablement for modulation in terms of increasing the binding of a ligand to an alpha 2M receptor and hence affecting receptor activity. In particular, the Examiner contends that the specification is silent with regard to how an agonist is to work or function as a modulator of an increase in receptor activity, and the Examiner contends that one skilled in the art would therefore be forced to determine what type of activity is required.

In response, Claim 31 has been amended to recite a method for using a compound which decreases the interaction of a first heat shock protein and an alpha (2) macroglobulin receptor. As such, the rejection of claims 31, 32, 77 and 79-81 is obviated. With respect to the rejection of remaining rejected claims 71, 75, 78, and 82-84, Applicants disagree with the rejection, for the reasons discussed herein below.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well know in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); see also DeGeorge v. Bernier, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover,* 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue

experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If, to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original).

In light of the legal standard discussed *supra*, Applicants submit that the instant application provides sufficient teaching to enable one of skill in the art to make and use the methods of the invention that encompass administering an agonist that increases alpha (2) macroglobulin receptor activity, without undue experimentation.

Applicants assert that the specification discloses numerous methods for measuring alpha (2) macroglobulin receptor activity, that include measuring increases in activity. As indicated in the specification, the receptor activity need not be a direct activity of the receptor, such as binding assays, but may also include indirect effects of downstream signaling events (see page 30, lines 7-12). Examples of assays that can be employed to measure such alpha (2) macroglobulin receptor activation are found throughout the specification, particularly section 5.2.2, see, *e.g.*, binding and/or labeling assays disclosed at page 29, lines 24-26, page 30, line 35 through page 34, line 25; assays for stimulation of cytotoxic T cells disclosed at page 36, line 20 through page 37, line 2; downstream signaling assays for alpha (2) macroglobulin receptor activation disclosed at page 34, line 36 to page 35, line 6; and antigen presentation assays disclosed at page 32, lines 7 to 19. Another assay for measuring the ability of the receptor to increase an innate immune response that can be employed is the cytokine release assay, taught at page 35, lines 3 and 4.

Two specific examples illustrate how increased activity of a receptor by an agonist can be measured and how agonists can increase receptor activation. First, procedures for

measuring chemotactic activity are taught at page 35, lines 1 to 2, and page 35, lines 7 to 26, particularly page 35, lines 15 through 23, wherein comparing the number of migrating cells to a control would is described, a technique that clearly can be used to measure an increase or decrease in activation of the receptor, including an increase caused by a receptor agonist. Second, assays for calcium ion concentration measurement are disclosed at page 35, line 27, through page 36, line 6. The specification discloses that ligand binding to alpha (2) macroglobulin receptor increases intracellular calcium ion concentration, and that an agonist increases intracellular calcium ion concentration (page 36, lines 4-5). Therefore, the specification provides support for methods for modeling an immune response using an agonist which increases alpha (2) macroglobulin receptor activity.

Given the ample description in the specification of assays which can be used to measure alpha (2) macroglobulin receptor activity, one of skill in the art does not need to know which agonists are capable of providing the desired effect. The skilled in the art could use routine assays to test a compound, such as any of the compounds described in section 5.2.3 (page 37, line 3, to page 40, line 8), and determine which compounds are capable of acting as agonists to increase alpha (2) macroglobulin receptor activity. Thus, one of skill in the art could routinely determine if an agonist increased alpha (2) macroglobulin receptor activity, without undue experimentation.

Claims 75 and 76 are further rejected under 35 U.S.C.§ 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with theses claims. The Examiner contends that the specification, while being enabling for activities associated with ligand binding to alpha (2) macroglobulin receptor, does not reasonably provide enablement for activities other than receptor-ligand interactions.

Applicants respectfully disagree with the Examiner's contentions and submit that the specification reasonably provides enablement for activities other than receptor-ligand interactions. For example, one skilled in the art can employ a labeled ligand uptake assay such as that taught at page 34 (lines 13 to 26) of the specification and administer a labeled ligand in the presence and absence of a test compound. It should thereby be possible for one skilled in the art, to identify compounds that do not interfere with binding of the ligand to the receptor, *i.e.,* do not affect receptor-ligand interactions, but rather inhibit or enhance the receptor process of transporting the labeled ligand (uptake) into the cell after binding has

occurred. Similarly, other assays described that measure intracellular effects could be utilized in a similar way. For example, the assays for calcium ion concentration measurement (disclosed at page 35, line 27 through page 36, line 6 of the specification) could be used. As described therein, calcium flux or mobilization can be easily measured in the presence and absence of a test compound and an alpha (2) macroglobulin receptor ligand by flow cytometry, providing discreet measurements that can be analyzed as ratios to determine the downstream effects of ligand binding.

Thus, the skilled artisan can use the routine assays disclosed in the specification to determine the downstream effects of ligand binding, since procedures for measuring such effects are clearly provided by the specification.

In view of the forgoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

3. THE REJECTION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 71, 76, 83 and 84 are rejected under 35 U.S.C. 102(b) as being anticipated by Pizzo *et al.* ("Pizzo"). The Examiner contends that an antigen-alpha 2M complex of Pizzo is a peptide of sorts that can bind to the alpha 2M receptor and modulate the receptor.

Claims 31 and 71 have been amended to exclude alpha 2M complexes such as those disclosed by Pizzo. Support for the amendments can be found at page 12, lines 13 to 20, of the specification as filed. Support for the proposition that claims can be properly amended to exclude a particular species of a genus can be found in *In re* Johnson, 194 U.S.P.Q. 187 (C.C.P.A. 1977). There the court considered the sufficiency under 35 U.S.C. § 112 of a specification in which a genus and several species were disclosed. The applicant claimed the genus while excluding two of the disclosed species in order to avoid the prior invention of another. The court reversed the decision of the Patent and Trademark Office Board of Appeals and held that an application which discloses a genus and several species provides sufficient support under Section 112 for claims excluding certain species in order to avoid a prior art rejection. Thus, the rejection is obviated by the amendments to the claims.

In view of the forgoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 102, and requests allowance of the pending claims.

CONCLUSION

Applicants respectfully request that the present amendment and remarks be made of record in the instant application. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

It is believed that no fee is required for filing this Amendment. In the event a fee is required, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: November 7, 2002

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Enclosures

EXHIBIT A
MARKED-UP VERSION OF THE AMENDED CLAIMS
U.S. Patent Application Serial No. 09/668,724
(Attorney Docket 8449-128)

31. (twice amended) A method for modulating an immune response comprising administering to a human a purified compound, [other than a complex of a heat shock protein and a peptide,] which [compound modulates] decreases the interaction of a first heat shock protein with the alpha (2) macroglobulin receptor, and is in an amount effective to modulate the immune response of said human, wherein the compound is other than a heat shock protein, a complex of a heat shock protein and a peptide, RAP, alpha (2) macroglobulin, or a complex of alpha (2) macroglobulin and a peptide.

71. (twice amended) A method for modulating an immune response comprising administering to a human a purified compound, [other than a complex of a heat shock protein and a peptide,] which [compound] binds to the alpha (2) macroglobulin receptor, in an amount effective to modulate [an] the immune response [in the mammal] of said human, wherein the compound is other than a heat shock protein, a complex of a heat shock protein and a peptide, RAP, alpha (2) macroglobulin, or a complex of alpha (2) macroglobulin and a peptide.